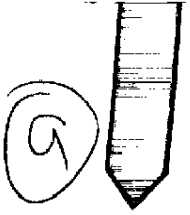

# 11th ARTIST Meeting, Singapore

**Presentation Dr. Kawamoto:**

Metabolites of pyrene ~~and naphthalene:~~ urinary 1-pyrenol (via 1-OH-pyrene, glucuronide)

Determination of urinary 1-pyrenol after glucoronidase treatment by HPLC with fluorescence detection; expressed per g creatinine.

Naphthalene metabolism via 2-naphthol to be determined by fluorescence detection after HPLC.

PAH: confounding by indoor air (e.g., from indoor kerosene heating in Korea) and food.

PAH, 1-pyrenol and 2-naphtol from indoor air (model room with kerosene heater): naphthalene in GVP, pyrene in both particle and GP phase; air measurements with impactor for PM10, PM2.5 and urethane foam for GVP; volunteers in test room for 12 h:

- Air pyrene higher with heater than without, no difference in PM10.
- Urinary 1-purenol increased but not stat. significant, high variability.
- Urinary 2-naphthol sign. increased with heating

Population study on 58 students in winter time, spot urine before lunch, questionnaire re heating and smoking:

- 2-naphthol 5-8 times higher in smokers as compared to non-smokers.

Population study on 251 workers and students for urinary 1-pyrenol:

- Meat and fish diet showed 2-3 times increase
- Smokers 2-3 times higher than non-smokers

Susceptibility markers of smoking:

- 1A1
- GSTM1
- NAT2
- 2A6

2A6 (in hu chromosome 19): *4: deletion, *1 wt, *2: Leu160His

Genotyping of 2A6: 4% of Japanese population showed homocygous deletion *4 / *4.

2A6 most important for nicotine oxidation:
5 wt and 6 homozygous deletion volunteer smoked for 1 h, then cotinine analysis in urine:

150 students and office workers: deletion genotype decreased cotinine significantly, no relation to smoking (cig./day).

650 healthy Japanese smokers, never smokers, ex-smokers, asked for number of cig./day as compared to homozygous 2A6 deletion: lower chance to start smoking, but indications that deletion reduces smoking cessation.

Cancer susceptibility:
Slightly reduced lung cancer risk for deletions (low stat. significance).

Possibility of OPG as a Biomarker:

In the past 3-4 years a large amount of data has accumulated to show the importance of a specific set of cytokine-cytokine receptor in maintaining bone homeostasis. This particular set refers to RANK-RANKL (receptor activator of NF-kappaB—Ligand) receptor-cytokine pair. RANKL is also known by the names TRANCE (TNF-related activation induced cytokine), or ODF (osteoclast differentiating factor), or osteoprotegerin ligand.

Association of RANKL with RANK triggers a cascade of signaling events that ultimately result in the activation and maturation of osteoclasts, cells that are responsible for bone degradation. This event is normally counter-balanced by bone generation through activity of osteoblasts (bone-forming cells), and / or through the production of OSTEOPROTEGERIN. Osteoprotegerin (OPG) is a soluble protein that has unique sequence similarity with RANKL, and acts as a decoy receptor to prevent or neutralize RANK-RANKL function (bone degradation).

Over-activation of RANK or RANKL and down regulation of OPG has been implicated in several diseases, including cancer (lung, breast, or prostrate cancer that do or do not metastasize to bone), stroke (due to arterial calcification) osteoporosis, asthma (steroid therapy for asthma activates RANKL synthesis, leading to bone loss), and other COPD.

As reviewed in the literature, smoking may influence disease outcomes listed above.

OPG, whose activation is inversely related with bone resorption, may be used as a Biomarker in the study of exposure to smoke in populations.

Qualities of OPG as a Biomarker:

1) Easily detectable in serum; also can be detected by PCR technology.
2) A protein whose function (or lack of function) might be related to several diseases, including cancer, COPD, and CVD.

A list of relevant abstracts and a review is attached.

Please contact Tapas for any questions or comments.

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